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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears a correction, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Signed Andrew Gregg

Dated 30 June 2003

Patents Form 1/77

UG02 E737645-1 D01030
P01/7700 0.00-0217780.6

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1/77

Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your Reference — **JTR/PF4905**

2. Patent application number *(The Patent office will fill in this part)* — **0217780.6**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

~~GLAXO GROUP LIMITED~~
~~GLAXOSMITHKLINE SERVICES UNLIMITED~~
~~980 GREAT WEST ROAD~~
~~BRENTFORD.~~
~~MIDDLESEX. TW8 9GS~~
~~GB~~

~~GLAXO WELLCOME HOUSE~~
~~BERKELEY AVENUE~~
~~GREENFORD~~
~~MIDDLESEX UB6 0NN~~

SMITHKLINE BEECHAN CORPORATION
ONE FRANKLIN PLAZA, PO BOX 7929
PHILADELPHIA, PA 19101-7929
USA

Patents ADP number *(if you know it)*
08111908002

If the applicant is a corporate body, give the country/state of its corporation
USA - PENNSYLVANIA

~~GB~~ AE
WO 9608

473664003

473587003

4. Title of the invention — **COMPOUNDS**

5. Name of your agent *(if you know one)* — **JANETTE ROWDEN**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE SERVICES UNLIMITED
CORPORATE INTELLECTUAL PROPERTY (CN9 25.1)
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX. TW8 9GS

Patents ADP number *(if you know it)* — 08268716002

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

See note (d)) — **YES**

9. Enter the number of sheets for any of the

Pat[illegible]s Form 1/77

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Description	17 ✓
Claim(s)	1 ✓ CF
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

J Rowden

Signature JANETTE ROWDEN 31 July 2002

AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON

020 8047 4493

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Compounds

This invention relates to novel triazole derivatives which are inhibitors of the transforming growth factor, ("TGF")-β signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

TGF-β1 is the prototypic member of a family of cytokines including the TGF-βs, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided in two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF-β signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF-β, ALK5, in the presence of TGF-β. The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production.

Activation of the TGF-β1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., *et al, N. Engl. J. Med.*, 1994; **331**(19), 1286-92. Further, TGF-β1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF-β1 receptor ALK5. Zhang Y., *et al, Nature*, 1998; **394**(6696), 909-13; Usui T., *et al, Invest. Ophthalmol. Vis. Sci.*, 1998; **39**(11), 1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF-β1 has been implicated in many renal fibrotic disorders. Border W.A., *et al, N. Engl. J. Med.*, 1994; **331**(19), 1286-92. TGF-β1 is elevated in acute and chronic glomerulonephritis Yoshioka K., *et al, Lab. Invest.*, 1993; **68**(2), 154-63, diabetic nephropathy Yamamoto, T., *et al*, 1993, *PNAS* **90**, 1814-1818., allograft rejection, HIV nephropathy and angiotensin-induced nephropathy Border W.A., *et al, N. Engl.*

J. Med., 1994; **331**(19), 1286-92. In these diseases the levels of TGF-β1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF-β1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF-β1 in vitro. Second, neutralizing anti-bodies against TGF-β1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF-β1 transgenic mice or in vivo transfection of the TGF-β1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., *et al*, *Lab. Invest.*, 1996; **74**(6), 991-1003. Thus, inhibition of TGF-β1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF-β1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty Saltis J., *et al*, *Clin. Exp. Pharmacol. Physiol.*, 1996; **23**(3), 193-200. In addition TGF-β1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF-β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., *et al*, *Atherosclerosis*, 1996; **120**(1-2), 221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF-β type II receptor ratio. Because TGF-β1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., *et al*, Jr., *J. Clin. Invest.*, 1995; **96**(6), 2667-75. TGF-β1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodeling via a TGF-β-dependent mechanism. Therefore, inhibiting the action of TGF-β1 on ALK5 is also indicated in atherosclerosis and restenosis.

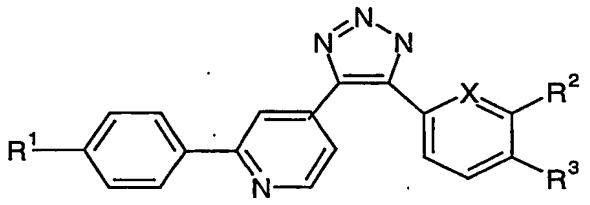
TGF-β is also indicated in wound repair. Neutralizing antibodies to TGF-β1 have been used in a number of models to illustrate that inhibition of TGF-β1 signaling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF-β1 and TGF-β2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., *J. Cell. Sci.*, 1995, **108**, 985-1002. Moreover, TGF-β antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., *Curr. Eye Res.*, 1998, **17**, 736-747, and accelerate wound healing of gastric ulcers in the rat, Ernst H., *Gut*, 1996, **39**, 172-175. These data strongly suggest that limiting the activity of TGF-β would be beneficial in many

tissues and suggest that any disease with chronic elevation of TGF-β would benefit by inhibiting smad2 and smad3 signaling pathways.

TGF-β is also implicated in peritoneal adhesions Saed G.M., *et al*, *Wound Repair Regeneration*, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

Surprisingly, it has now been discovered that a class of novel triazole derivatives function as potent and selective non-peptide inhibitors of ALK5 kinase and therefore, have utility in the treatment and prevention of various disease states mediated by ALK5 kinase mechanisms, such as chronic renal disease, acute renal disease, wound healing, arthritis, ósteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, for example, hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis, and restenosis.

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof:



(I)

wherein X is N or CH;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^4R^5$, $-(CH_2)_nR^4R^5$, $-O(CH_2)_nOR^4$, $-O(CH_2)_nNR^4R^5$, $-CONR^4R^5$, $-CO(CH_2)_nNR^4R^5$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^5SO_2R^5$ and $-NR^4COR^5$;

R^2 is selected from H, C_{1-6}alkyl, halo, CN or perfluoroC_{1-6}alkyl;

R^3 is selected from H or halo;

R^4 and R^5 are independently selected from H or C_{1-6}alkyl; or R^4R^5 together with the atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl and C_{1-6} alkoxy;and
n is 1-4.

Preferably, X is N.

Preferably, R^2 is H, C_{1-6}alkyl or halo. More preferably, R^2 is H, methyl, chloro or fluoro.

Preferably, R^3 is H or fluoro.

Preferably, R^4 and R^5 are independently H or methyl, or R^4R^5 together with the atom to which they are attached form a 3, 4, 5, 6 or 7 membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substitutents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy.

Suitably, R^4R^5 together with the atom to which they are attached form a morpholine, piperidine, pyrrolidine, piperazine, N-methyl piperazine, imidazole or N-methyl imidazole ring.

It will be appreciated that the present invention is intended to include compounds having any combination of the preferred groups listed hereinbefore.

Compounds of formula (I) which are of special interest as agents useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF-β are:
2-(4-Methanesulfonyl-phenyl)-4-(5-(6-methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridine;
2-(4-Fluoro-phenyl)-4-(5-(6-methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridine;
2-(4-Methoxy-phenyl)-4-(5-(6-methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridine;
4-[4-(5-(6-Methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridin-2-yl]-N-(tetrahydro-pyran-4-yl)-benzamide;
4-{4-[4-(5-(6-Methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridin-2-yl]-benzyl}-morpholine;
and pharmaceutically acceptable salts, solvates and derivatives thereof.

The present invention also covers the pharmaceutically acceptable salts of the compounds of formula (I). Suitable pharmaceutically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

The terms "C_{1-6}alkyl" and "C_{1-7}alkyl" as used herein, whether on their own or as part of a group, refers to a straight or branched chain saturated aliphatic hydrocarbon radical of 1 to 6 and 1 to 7 carbon atoms respectively, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl and hexyl.

The term "alkenyl" as a group or part of a group refers to a straight or branched chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number(s) of carbon atoms. References to "alkenyl" groups include groups which may be in the E- or Z-form or mixtures thereof.

The term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy.

The term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical containing the specified number(s) of carbon atoms, preferably from 5 to 14 carbon atoms, and more preferably from 5 to 10 carbon atoms, which may include bi- and tricyclic systems, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy. Such aryl groups include cyclopentadieny, phenyl or naphthyl.

The term "aryloxy" as a group or part of a group refers to an aryl ether radical, wherein the term "aryl" is defined above.

The term "cycloalkyl" as a group or part of a group refers to a saturated carbocyclic radical containing the specified number of carbon atom(s), preferably from 3 to 14 carbon atoms, more preferably 3 to 10 carbon atoms, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy. Such groups in particular include cyclopropyl,cyclobutyl, cyclopentyl and cyclohexyl.

The terms "heterocyclyl" as a group or a part of a group refers to a stable saturated or partially saturated (i.e. non-aromatic) 3 to 6 membered monocyclic ring containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy.

The term "het" or "heteroaryl" as a group or part of a group refers to a stable heterocyclic aromatic 6 to 14 membered monocyclic ring containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-4} alkyl and C_{1-4} alkoxy. Suitably the 6 to 14-membered heterocyclic moiety is selected from furan, dioxolane, thiophene, pyrrole, imidazole, pyrrolidine, pyran, pyridine, pyrimidine, morpholine, piperidine, oxazole, isoxazole, oxazoline, oxazolidine, thiazole, isothiazole, thiadiazole, benzofuran, indole, isoindole, quinazoline, quinoline, isoquinoline and ketal.

The term "heteroaryloxy" as a group or part of a group refers to a heteroaryl ether radical, wherein the term "heteroaryl" is defined above.

The term "perfluoroalkyl" as used herein includes compounds such as trifluoromethyl.

The term "perfluoroalkoxy" as used herein includes compounds such as trifluoromethoxy.

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

As used herein the term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compound of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) the a compound of formula (I) or an active metabolite or residue thereof, eg, a prodrug. Preferred pharmaceutically acceptable derivatives according to the invention are any pharmaceutically acceptable salts, solvates or prodrugs.

The term "ALK5 inhibitor" is used herein to mean a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

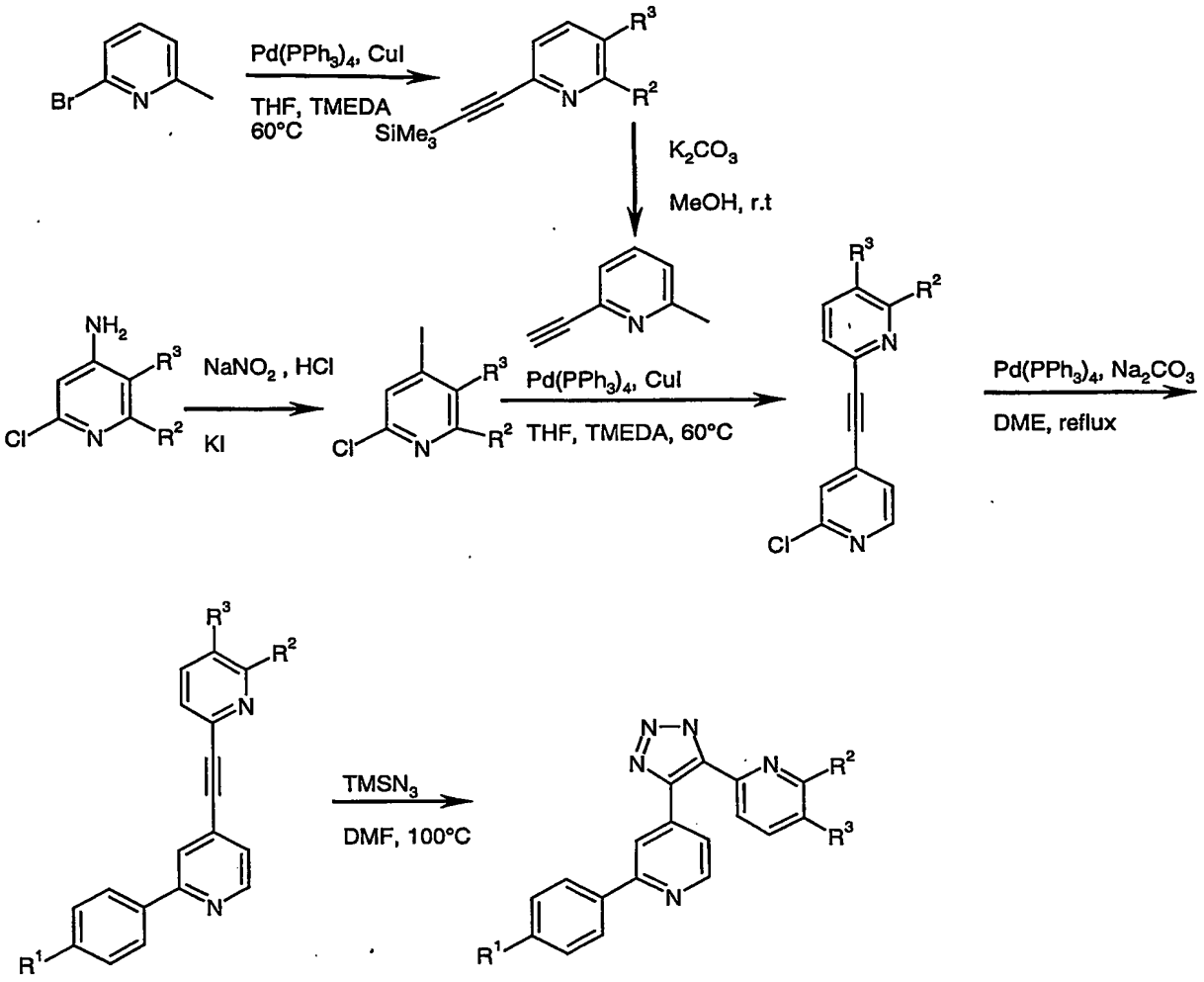
The term "ALK5 mediated disease state" is used herein to mean any disease state which is mediated (or modulated) by ALK5, for example a disease which is modulated by the inhibition of the phosphorylation of smad 2/3 in the TGF-1ß signaling pathway.

The term "ulcers" is used herein to include, but not to be limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

The compounds of formula (I) can be prepared by art-recognised procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Specifically, compounds of formula (I) may be prepared as illustrated in Scheme 1.

Scheme 1



Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts thereof.

The compounds of the present invention have been found to inhibit phosphorylation of the Smad-2 or Smad-3 proteins by inhibition of the TGF-β type I (ALK5) receptor.

Accordingly, the compounds of the invention have been tested in the assays described herein and have been found to be of potential therapeutic benefit in the treatment and prophylaxis of disorders characterised by the overexpression of TGF-β.

Thus, there is provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate or derivative thereof, for use as a medicament in human or veterinary medicine, particularly in the treatment or prophylaxis of disorders characterised by the overexpression of TGF-β.

It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions. It will further be appreciated that references herein to treatment or prophylaxis of disorders characterised by the overexpression of TGF-β, shall include the treatment or prophylaxis of TGF-β associated disease such as fibrosis, especially liver and kidney fibrosis, cancer development, abnormal bone function and inflammatory disorders, and scarring.

Other pathological conditions which may be treated in accordance with the invention have been discussed in the introduction hereinbefore. The compounds of the present invention are particularly suited to the treatment of fibrosis and related conditions.

Compounds of the present invention may be administered in combination with other therapeutic agents, for example antiviral agents for liver diseases, or in combination with ACE inhibitors or Angiotensin II receptor antagonists for kidney diseases.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.

ALK5-mediated disease states, include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis, kidney fibrosis, liver fibrosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids and restenosis.

According to a further aspect of the present invention there is provided a method of inhibiting the TGF-β signaling pathway in mammals, for example, inhibiting the

phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

According to a further aspect of the present invention there is provided a method of inhibiting matrix formation in mammals by inhibiting the TGF-β signalling pathway, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

The pharmaceutically effective compounds of formula (I) and pharmaceutically acceptable salts thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example

lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage

corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

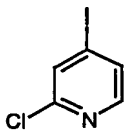
The following non-limiting examples illustrate the present invention.

Abbreviations

DMF – Dimethylformamide
EtOAc – Ethyl acetate
MeOH – methanol
TMS – trimethylsilyl
THF – tetrahydrofuran
TMEDA – N,N,N',N'- Tetramethylethylenediamine

INTERMEDIATES

Intermediate 1 : 2-Chloro-4-iodo-pyridine

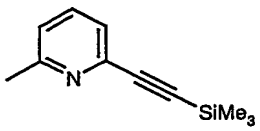


A solution of 4-amino-2-chloro-pyridine (8.09g, 63 mmol, 1eq) in water (150mL) was cooled at 0°C , followed by addition of concentrated 98% HCl . A solution of sodium nitrite (5.65g, 82mmol, 1.3eq) in water (50mL) was added slowly at –10°C. The

mixture was stirred at this temperature for 40 min, and a solution of potassium iodide (12.55g, 75.6mmol, 1.2eq) in water (50mL) was added. The resulting mixture was stirred at 0°C overnight. After treatment with NaOH 35%, and extraction with ethyl acetate, the organic phases were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (eluent : CH_2Cl_2 then CH_2Cl_2/ CH_3OH 99/1) to give the title compound as an orange solid (9.5g, 63%).

^1H NMR (300 MHz, $CDCl_3$) δ: 7.99 (1H, d), 7.68 (1H, s), 7.52 (1H, d).
(GC-MS) m/z : 239

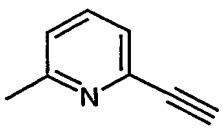
Intermediate 2 : 2-Methyl-6-trimethylsilanylethynyl-pyridine



To a solution of 2-bromo-4-methyl-pyridine (25g, 0.15 mol) in dry THF (200mL), were added TMEDA (200mL) and TMS-acetylene (100mL, excess) under N_2.The resulting mixture was degassed with nitrogen for 10 min, then tetrakis triphenylphosphine palladium (3.7mmol, 4.3g) and copper iodide (14.7mmol, 2.8g) were added. The resulting mixture was heated at 60°C for 18h. The reaction mixture was concentrated and the residue partitioned between ethyl acetate / water. The organic phase was dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude product which was purified by chromatography on silica gel (CH_2Cl_2) to give the title compound (18.4g, 65%) as a black oil.

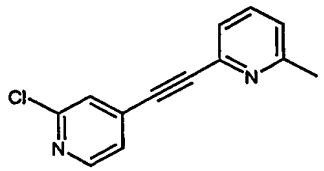
^1H NMR (300 MHz, $CDCl_3$) δ: 7.58-7.49 (1H, m), 7.30 (1H, d), 7.10 (1H, d), 2.56 (3H, s), 0.28 (9H, s).

Intermediate 3 : 2-Ethynyl-6-methyl-pyridine



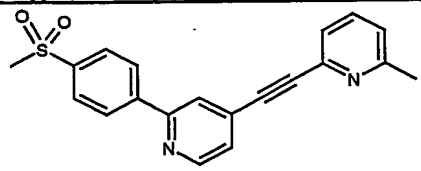
To a solution of Intermediate 2 (18.4g, 0.097mol) in MeOH (100 ml) was added potassium carbonate (4eq, 0.39mol, 53.7g). The reaction mixture was then stirred at rt for 30 min and the solvent evaporated to dryness. The residue was partitioned between ethyl acetate / water. The organic layer was dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure to give the title compound (8.75g, 77%) as a brown oil.
^1H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.34 (1H, m), 7.14 (1H, d), 6.98 (1H, d), 2.97 (1H, s), 2.40 (3H, s).

Intermediate 4 : 6-Methyl-2-[(2-chloro-pyridin-4-yl)-ethynyl]-pyridine



To a solution of 2-chloro-4-iodo-pyridine (Intermediate 1) (1.85g, 7.74mmol) in dry THF (40mL) were added under nitrogen, TMEDA (20mL) and intermediate 3 (1.1eq, 1g, 8.51mmol). The resulting mixture was degassed with nitrogen for ten mins, then tetrakis triphenylphosphine palladium (0.464mmol, 537mg) and copper iodide (0.928 mmol, 177mg) were added. The resulting mixture was heated at 60°C for 4h. The mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and filtered. Solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc 90:10) to afford the title compound as a beige solid (1.54g, 86.4%).
^1H NMR (300 MHz, $CDCl_3$) δ: 8.29 (1H, d), 7.52 (1H, t), 7.39 (1H, s), 7.34-7.24 (2H, m), 7.10 (1H, d), 2.50 (3H, s).

Intermediate 5: 6-Methyl-2-[(2-methylsulfonyl-pyridin-4-yl)-ethynyl]-pyridine

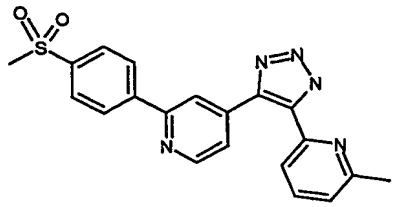


Intermediate 4 (1g, 4.37mmol) and 4-(methylsulfonyl)phenyl boronic acid (1.14g, 5.7 mmol),were dissolved in a mixture of toluene (30mL) and ethanol (10mL). To this solution were added tetrakis(triphenylphosphine) palladium (0.118 g, 0.1mmol) and aqueous sodium carbonate 2M (8.6mL, 17.2mmol) under nitrogen. The resulting mixture was stirred under reflux for 6 h. The mixture was hydrolysed with water and extracted with ethyl acetate, the combined organic phases were washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure . The crude product was purified by chromatography on silica gel (eluent : CH_2Cl_2/CH_3OH 98:2) to give the title compound as a yellow oil (0.7g, 46%).

^1H NMR (300 MHz, $CDCl_3$) δ: 8.66 (1H, d), 8.14 (2H, d), 7.98 (2H, d), 7.90 (1H, s), 7.56 (1H, t), 7.43-7.32 (2H, m), 7.12 (1H, d), 3.03 (3H, s), 2.50 (3H, s).
(APCI) m/z : 349 (MH^+)

EXAMPLES

Example 1 : 2-(4-Methanesulfonyl-phenyl)-4-(5-(6-methyl)-pyridin-2-yl-1H-[1,2,3]triazol-4-yl)-pyridine



To a solution of Intermediate 5 (700mg, 2 mmol) in dry DMF (13 ml) was added azidotrimethylsilane (8 mmol, 930mg). The reaction mixture was then stirred at 100°C overnight. The reaction mixture was hydrolysed with water and extracted with CH_2Cl_2 . The organic phase was washed with water, dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* gave a crude product which was purified by chromatography on silica gel (toluene / isopropylamine 95:5). The crude oil was precipitated in a mixture CH_2Cl_2/hexane to give the title compound as a yellow powder (260mg, 33.2%), gummy at 150°C.

^1H NMR (300 MHz, $CDCl_3$) δ: 8.70 (1H, d), 8.28 (1H, s), 8.15 (2H, d), 7.95 (2H, d), 7.70-7.57 (2H, m), 7.50 (1H, d), 7.15 (1H, d), 3.00 (3H, s), 2.50 (3H, s), NH triazole not observed.
Calcd. Mass for $C_{20}H_{17}N_5O_2S$ (MH+):392.1181. Found (H.R.M.S): 392.1218

BIOLOGICAL DATA

The biological activity of the compounds of the invention may be assessed using the following assays:

Assay 1 (Cellular transcriptional assay)

The potential for compounds of the invention to inhibit TGF- β signaling may be demonstrated, for example, using the following *in vitro* assay.

The assay was performed in HepG2 cells stably transfected with the PAI-1 promoter (known to be a strong TGF-β responsive promoter) linked to a luciferase (firefly) reporter gene. The compounds were selected on their ability to inhibit luciferase activity in cells exposed to TGF-β. In addition cells were transfected with a second luciferase (Renilla) gene which was not driven by a TGF-β responsive promoter and was used as a toxicity control.

(96 well-)microplates are seeded, using a multidrop apparatus, with the stably transfected cell line at a concentration of 35000 cells per well in 200 µl of serum-containing medium. These plates are placed in a cell incubator.

18 to 24 hours later (Day 2), cell-incubation procedure is launched. Cells are incubated with TGF-β and a candidate compound at concentrations in the range 50 nM to 10 μM (final concentration of DMSO 1%). The final concentration of TGF-β (rhTGFβ-1) used in the test is 1 ng/mL. Cells are incubated with a candidate compound 15-30 mins prior to the addition of TGF-β. The final volume of the test reaction is 150 μl. Each well contains only one candidate compound and its effect on the PAI-1 promoter is monitored.

Columns 11 and 12 are employed as controls. Column 11 contains 8 wells in which the cells are incubated in the presence of TGF-β, *without* a candidate compound. Column 11 is used to determine the 'reference TGF-β induced firefly luciferase value' against which values measured in the test wells (to quantify inhibitory activity) may be compared. In wells A12 to D12, cells are grown in medium without TGF-β. The firefly luciferase values obtained from these positions are representive of the 'basal firefly luciferase activity'. In wells E12 to H12, cells are incubated in the presence of TGF-β and 500 μM CPO (Cyclopentenone, Sigma), a cell toxic compound. The toxicity is revealed by decreased firefly and renilla luciferase activities (around 50 % of those obtained in column 11).

12 to 18 hours later (day 3), the luciferase quantification procedure is launched. The following reactions are performed using reagents obtained from a Dual Luciferase Assay Kit (Promega). Cells are washed and lysed with the addition of 10 μl of passive lysis buffer (Promega). Following agitation (15 to 30 mins), luciferase activities of the plates are read in a dual-injector luminometer (BMG lumistar). For this purpose, 50 μl of luciferase assay reagent and 50 μl of 'Stop & Glo' buffer are injected sequentially to quantify the activities of both luciferases. Data obtained from the measurements are processed and analysed using suitable software. The mean Luciferase activity value obtained in wells A11 to H11 (Column 11, TGF-βonly) is considered to represent 100% and values obtained in wells A12 to D12 (cells in medium alone) give a basal level (0%). For each of the compounds tested, a concentration response curve is constructed from which an IC_{50} value can be determined graphically.

Assay 2 (Alk5 Fluorescence Polarization Assay)

Kinase inhibitor compounds, conjugated to fluorophores, can be used as fluorescent ligands to monitor ATP competitive binding of other compounds to a given kinase. The increase in depolarization of plane polarized light, caused by release of the bound ligand into solution, is measured as a polarization/anisotropy value. This protocol details the use of a rhodamine green-labeled ligand for assays using recombinant GST-ALK5 (residues 198-503).

Assay buffer components: 62.5 mM Hepes pH 7.5 (Sigma H-4034), 1 mM DTT (Sigma D-0632), 12.5 mM $MgCl_2$ (Sigma M-9272), 1.25 mM CHAPS (Sigma C-3023)

Protocol: Solid compound stocks were dissolved in 100% DMSO to 1 mM and transferred into column 1, rows A-H of a 96-well, U bottom, polypropylene plate (Costar #3365) to make a compound plate. The compounds were serially diluted (3-fold in 100% DMSO) across the plate to column 11 to yield 11 concentrations for each test compound. Column 12 contains only DMSO. A Rapidplate™-96 was used to transfer 1 µl of sample from each well into a 96-well, black, U bottom, non-treated plate (Costar #3792) to create an assay plate. These assay plates are ready for adding reagents.

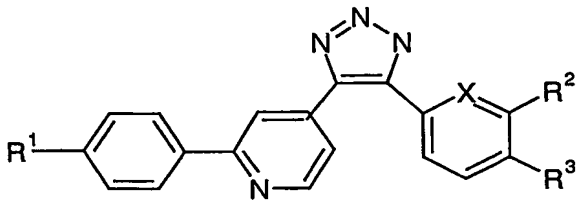
ALK5 was added to assay buffer containing the above components and 1 nM of the rhodamine green-labelled ligand so that the final ALK5 concentration was 10 nM based on active site titration of the enzyme. 39 µl of the enzyme/ligand reagent was added to each well of the previously prepared assay plates. A control compound(1 µl) was added to column 12, rows E-H for the low control values. The plates were read immediately on a LJL Acquest fluorescence reader (Molecular Devices, serial number AQ1048) with excitation, emission, and dichroic filters of 485nm, 530 nm, and 505 nm, respectively. The fluorescence polarization for each well was calculated by the Acquest reader and then imported into curve fitting software for construction of concentration response curves. The normalized response was determined relative to the high controls (1 µl DMSO in column 12, rows A-D) and the low controls (1 µl of control compound in column 12, rows E-H). An IC_{50} value was then calculated for each compound.

The compounds of this invention generally show ALK5 receptor modulator activity having IC_{50} values in the range of 1 to 100nM and TGF-β cellular activity having IC_{50} values in the range of 0.0001 to 10µM.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, the following claim:

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof:



(I)

wherein X is N or CH;

R^1 is selected from H, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, halo, cyano, perfluoro C_{1-6}alkyl, perfluoroC_{1-6}alkoxy, $-NR^4R^5$, $-(CH_2)_nR^4R^5$, $-O(CH_2)_nOR^4$, $-O(CH_2)_nNR^4R^5$, $-CONR^4R^5$, $-CO(CH_2)_nNR^4R^5$, $-SO_2R^4$, $-SO_2NR^4R^5$, $-NR^5SO_2R^5$ and $-NR^4COR^5$;

R^2 is selected from H, C_{1-6}alkyl, halo, CN or perfluoroC_{1-6}alkyl;

R^3 is selected from H or halo;

R^4 and R^5 are independently selected from H or C_{1-6}alkyl; or R^4R^5 together with the atom to which they are attached form a 3, 4, 5, 6 or 7-membered saturated or unsaturated ring which may contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, $-CF_3$, -OH, $-OCF_3$, C_{1-6} alkyl and C_{1-6} alkoxy;and

n is 1-4.